REMARKS

The Examiner's Office Action of July 3, 2003 has been received and carefully reviewed. Initially, it is noted that the Examiner's acknowledgement of Applicant's earlier election of Group I, claims 1-4 and 13-14 is appreciated. As originally filed, the present application contained claims 1-53, of which claims 5-12 and 15-53 were canceled without prejudice or disclaimer. Prior to this amendment, claims 1-4 and 13-14 were pending in the application. By this amendment, claims 1-4 and 13-14 are canceled and new claims 54-91 are added, of which claims 54 and 77 are independent. The new claims are directed to methods of detecting an acid resistant microorganism with monoclonal antibodies. The non-elected provisions of detecting acid resistant microorganisms with aptamers are excluded.

For the Examiner's convenience, Applicant respectfully notes that new claims 54-57 are based on canceled claims 1-4; new claims 58-61 are based on canceled claims 5-8; new claims 62-63 are based on canceled claims 26 and 28; new claim 64 is based on canceled claim 17; new claims 65-66 are based on canceled claims 18 and 20; new claim 67 is based on canceled claim 15; new claim 68 is based on canceled claim 9; new claims 69-70 are based on canceled claim 10; new claims 71-72 are based on canceled claims 22 and 24; new claim 73 is based on canceled claim 16; new claim 74 is based on canceled claims 33 and 34; new claim 75 is based on canceled claims 36-39; new claim 77 is based on canceled claim 13; new claims 78-82 find the same basis as new claims 62-67, noted above; new claim 84 is based on canceled claim 14; and new claims 85-91 find the same basis as new claims 71-75 noted above. All of these new claims, therefore, are supported by the original disclosure.

For the reasons discussed in detail below, Applicants believe that the application is now in condition for allowance.

I. Claim Objections

By the present Office Action, claims 1-4 and 13-14 were objected to for reciting non-elected aptamers. Claims 1-4 and 13-14 are hereby canceled. Accordingly, it is respectfully submitted that this objection is moot. New claims 54-91 are directed only to the subject matter of the elected Group I.

II. Sequence Listings

As required, Applicant has amended the application and drawings to include sequence identification tags to all amino acid sequences of at least 4 amino acid and all nucleotide sequences of at least 10 nucleotides. Corrected formal drawings are submitted herewith.

III. Claim Rejections under 35 U.S.C. 112, first paragraph

Claims 1-4 and 13-14 were rejected under 35 U.S.C. 112, first paragraph, on the basis that the claimed method for detecting an infection of an acid-resistant microorganism in stool with a monoclonal antibody or "fragment or derivative thereof" was not described in the specification in such a way to enable one skilled in the art to make and/or use the invention. Applicant respectfully disagrees.

The claimed invention is directed to a method for detecting an infection with an acid-resistant microorganism, particularly with *Helicobacter*, in a mammal, wherein stool is used for the determination. Using the claimed invention detection of infection with an acid-resistant microorganism can be accomplished without the use of body fluids, for which invasive techniques are necessary. Microorganisms sought to be detected are those that survive in the stomach due to their acid-resistance, but which are nevertheless degraded in the intestine. Heretofore it has been difficult to detect antigens which are still determinable after passing through the intestine. The claimed invention solves this problem by using at least two different monoclonal antibodies which bind to epitopes of two different antigens, such that the formation of at least one antigen-antibody complex is detected. By using two different monoclonal antibodies, or even fragments or derivatives of monoclonal antibodies which can specifically bind to epitope, e.g., Fab, $F(ab')_2$ or Fv-fragments, the presence of acid-resistant microorganisms can be detected in highly reliable manner.

Specifically, the invention, as recited in new independent claim 54, is directed to:

> A method for detecting an infection of an acid-resistant microorganism in a mammal comprising: (a) incubating a stool sample of a the mammal with at least two different monoclonal antibodies, fragments or derivatives thereof under conditions allowing formation of complexes between antigens from the acid-resistant organisms and the antibodies, fragments or derivatives thereof, in which (aa) a first monoclonal antibody or fragment or derivative thereof <u>specifically binds an epitope of a first antigen</u>, which shows at least with some mammals a structure after intestinal passage that corresponds to

a native structure, or a structure which a mammal produces antibodies against after being infected or immunized with the acid resistant microorganism, an extract or lysate thereof, protein therefrom, a fragment thereof or synthetic peptide; (ab) a second monoclonal antibody or fragment or derivative thereof specifically binds an epitope of a second antigen, differing from the epitope of the first antigen, which shows at least with some mammals a structure after intestinal passage that corresponds to the native structure, or a structure which a mammal produces antibodies against after being infected or immunized with the acid-resistant microorganism, an extract or lysate thereof, a protein therefrom, a fragment thereof or a synthetic peptide, in which the groups of mammals according to (aa) and (ab) may overlap, and in total essentially make up the overall number of infected, mammals, and (b) detecting the formation of at least one antigen-antibody complex according to (aa) or (ab).

New independent claim 77, is directed to:

A method for detecting an infection with *Helicobacter pylori* in the stool of a mammal, in which: (aa) a first monoclonal antibody, fragment or derivative thereof specifically binds ß-urease or a fragment thereof; (ab) a second monoclonal antibody, fragment or derivative thereof specifically binds the 26kDa-antigen or a fragment thereof or specifically binds Hsp60 or fragment thereof, and (b) detecting the formation of at least one antigen-antibody complex set out in (aa) or (ab).

Contrary to the Examiner's suggestion, not "every" antibody fragment or derivative is claimed, but only those antibodies or fragments or derivatives thereof which "specifically bind to an epitope of a first antigen" or a "second antigen", respectively, as recited in claim 54; or which "specifically binds" to ß-urease" and 26kDa-antigen or Hsp60, as recited in claim 77. It is evident, therefore, that neither a single amino acid nor a combination of CDRs which are not in the proper orientation will bind to the epitope. Moreover, the written description clearly describes "fragments" and how they can be obtained. Examples for derivatives, as well as methods how to obtain them is also adequately set forth in the description (See e.g., page 7, last paragraph). Further, the claims specifically require that fragments and derivatives are required to have certain binding specificities, i.e. that they should bind specifically to an epitope having a structure after intestinal passage corresponding to a native structure, or an epitope having an immunogenic structure. These binding specificities are also adequately set forth in the specification. (See e.g., specification, pages 8-9). The specification also provides that "fragments" or "derivatives" of monoclonal antibodies have the same binding specificity

as monoclonal antibodies (See e.g., specification, page 7, last paragraph). Indeed, fragments of antibodies are well known in the art and their properties and methods for producing them are, for example, described in Harlow & Lane, a reference which is repeatedly cited throughout the specification. It is respectfully submitted, therefore, that the specification clearly provides the properties that such fragments and derivatives should have in order to be suitable for use in the methods of the invention.

The Examiner's further contends that, for a given antibody, six CDR's may not be in their proper orientation and thus will not necessarily translate into a functioning antibody. It is respectfully submitted, however, that CDR's that do not translate into an antibody binding to an epitope with the binding properties as defined in claims 54 and 77, are within the claimed invention. Indeed, those of ordinary skill know that not any fragment or derivative of any monoclonal antibody is usable, but that such fragments and derivatives are required to have certain properties. These properties are clearly set out in the claims and are explained in detail in the specification. The specification further describes various examples of suitable fragments and derivatives, as well as information on how such fragments and derivatives may be obtained. Moreover, as noted above, the specification provides numerous references to a standard text. No undue experimentation would be imposed on one of ordinary skill to achieve the methods as set out in the claim.

In further support of the rejection, the Examiner, citing Rudinger *et al*, "Peptide Hormones" edited by Parsons et al, University Park Press, June 1976, pages 1-7, proposes that that "the significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted, but must be determined from case to case by painstaking experimental study." From this the Examiner concludes that recitation of "derivative" is non-enabling since, "retaining affinity while freely substituting amino acids is simply unpredictable." Applicant submits, however, that the cited Rudinger *et al.* article, which was published in 1976, is outdated. Today, one of ordinary skill can now easily determine using competition experiments, for example, whether a particular binding agent binds to the same epitope as another. Thus, it is not wholly necessary for the CDR's to be determined.

In view of the foregoing, it is respectfully submitted that there is no lack of guidance, lack of examples or lack of predictability with regard to producing and using the

derivatives of the claimed invention. In fact, Example 10 in the specification describes in detail how to determine the CDR's of a particular monoclonal antibody. Accordingly, if required, the skilled person could readily determine the CDR's of a monoclonal antibody, and also could determine if these were present in the fragment concerned, without undue experimentation.

Claims 1-4 and 13-14 were also rejected under 35 U.S.C. 112, first paragraph, on the basis that claimed method for detecting an infection of an acid-resistant microorganism in the stool wherein the monoclonal antibody binds "an epitope of the first antigen" and "an epitope of a second antigen" and binds ß-urease "fragments" or 26 kDa "fragments" or Hsp60 "fragments", is not described in the specification in such as way to enable one of ordinary skill in the art to make or use the invention. In particular, the Examiner contends that one of skill in the art would be forced into excessive experimentation to identify which "fragments" are able to mimic the required secondary and tertiary structure of the full length polypeptide, and which fragments are capable of complexing with the monoclonal antibody that recognizes the full length polypeptide. These considerations, however, are misdirected, as they do not relate to the claimed invention.

Generally, the claimed invention is directed to the use of antibodies which bind to epitopes that survive the intestine and are present in the stool. The invention uses a first monoclonal antibody binding an epitope of a first antigen and a second monoclonal antibody binding an epitope of the second antigen wherein ß-urease can be one of the antigens. The significant feature is that antibodies are used which bind to a structure that corresponds to the native structure after intestinal passage or the structure which a mammal produces antibodies against after being infected, i.e. a structure which is presented to the immune system after infection. These structures can be fragments of the organism or linear polypeptides or short three-dimensional structures, provided they survive the intestinal passage. The method of the invention does not require the identity of fragments which are able to mimic secondary or tertiary structures of the full length polypeptide, but only to use the antibodies which bind to epitopes which survive the intestine and are present in the stool. The specification and examples therein clearly teach that such monoclonal antibodies are known.

Thus, contrary to the Examiner's suggestion, it is not necessary to determine which linear segments of a protein are accessible to the host's immune system, as this is not relevant to the claimed method. It is also not necessary to mimic conformational structures of determinants or full length proteins because these will not be present in the stool after the intestinal passage. The claims of the application specify the use of monoclonal antibodies which bind a particular defined polypeptide "or fragment thereof." Therefore, the claims cover use of either type of antibody and it is only relevant if that polypeoptide or fragments is present in fecal samples. Particularly, the claimed invention does not require that the same monoclonal antibody recognizes both the particular fragment as well as the full length polypeptide. Furthermore, the determination of whether a monoclonal antibody binds to a peptide "fragment" does not require a knowledge of the secondary or tertiary structure of the polypeptide from which it is derived. It is a simple matter for one of ordinary skill to determine whether a monoclonal antibody binds to a peptide using antibody binding assays, which are well known and routinely practiced in the art.

Indeed, it is well within the abilities of those of ordinary skill to produce "fragments" of a particular polypeptide. First, peptide "fragments" are produced by protease digestion using proteases well known in the art with cleavage sites, such as trypsin, papain etc. Fragments can also be produced using known chemical treatment techniques, for example, boiling the polypeptide in acid conditions, or by creating synthetic peptides using peptide synthesis machinery, based on the sequence of the polypeptide from which the fragment is derived. Once these peptide fragments are constructed, they may then be tested in an antibody binding assay, which as noted above, is a technique well known in the art.

The specification, in Example 6, describes in detail a preferred binding assay, namely the "epitope binding assay." As described, the peptide fragments may be bound or coupled to a solid phase, treated with the monoclonal antibody, and bound antibodies detected. Using this assay, it is possible to determine whether a particular peptide fragment contains the epitope, and whether it must necessarily bind monoclonal antibody. The specification clearly contains an enabling disclosure of monoclonal antibodies which

bind to the specific polypeptides, as well as those which bind to fragments of such polypeptides.

In view of the foregoing, it is respectfully submitted that new independent claims 54 and 77 satisfy the requirements of 35 U.S.C. 112, first paragraph. Accordingly, it is respectfully requested that the Examiner's rejection to the subject matter of these claims be reconsidered and withdrawn. Inasmuch as the foregoing arguments apply to claims 55-73 and 75-91 by virtue of their dependency on independent claims 54 and 77, respectively, it is respectfully submitted that the Examiner's rejection to the subject matter of these claims also be reconsidered and withdrawn.

IV. Claim Rejections Under 35 U.S.C. 112, second paragraph

Claim 1-4 and 13-14 were also rejected under 35 U.S.C. 112, second paragraph, on the basis that use of the phrase "derivative" renders the claims vague and indefinite, "since it is unclear if the monoclonal antibody or fragment are undergoing any kind of chemical modification as implied by the recitation of 'derivative'." Moreover, it is contended that there is no way for a person of skill in the art to ascribe a discrete and identifiable definition to the "phrase" derivative, since it is unclear how the monoclonal antibodies or fragment are derived as referred to in the claims.

As specifically outlined in Applicant's above arguments with respect to the rejections under 35 U.SC. 112, first paragraph, Applicant submits that this phrase is not unclear, but rather well defined, and methods for obtaining derivates are adequately disclosed in the application.

Accordingly, it is respectfully requested that the Examiner's rejection to the subject matter of these claims be reconsidered and withdrawn. Inasmuch as the foregoing arguments apply to claims 55-73 and 75-91 by virtue of their dependency on independent claims 54 and 77, respectively, it is respectfully submitted that the Examiner's rejection to the subject matter of these claims also be reconsidered and withdrawn.

V. Claim Rejections Under 35 U.S.C. 102(b)

Claims 1-4 were rejected under 35 U.S.C. 102(b) as being anticipated by the disclosure of U.S. Patent No. 5,932,430 to Larka et al. ("Larka"). 35 U.S.C. 102(b)

provides that a person may be entitled to a patent unless the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than a year prior to the date of the application for patent in the United States. The present application claims priority to PCT/EP99/08212 filed October 29, 1999, EP 98 120687.3 filed November 6, 1998, and EP 98 120517.2 filed October 29, 1998. Larka was not published until April 3, 1999, less than one year from the effective filing date of the present application. Larka, therefore, is not a proper reference under 35 U.S.C. 102(b).

Even if Larka were citable under 35 U.S.C. 102(b), Applicant submits that Larka, nevertheless, fails to anticipate and/or render obvious the claimed invention. First, Applicant notes that the method of Larka requires the use of two polyclonal antibodies which bind to the same antigen. Unlike the claimed invention, however, Larka does not teach a method for detecting an infection of an acid-resistant microorganism wherein, *inter alia*, a first monoclonal antibody specifically binds an epitope of a first antigen, and a second monoclonal antibody which specifically binds an epitope of a second antigen. Indeed, it is the use of at least two different antigens that provides for the increased reliability offered by the method of the claimed invention and which allows for the significantly increased probability of detecting an infection even if one of both antigens is not detectable for an individual. These advantages are illustrated in Example 9 and Table 4 of the specification.

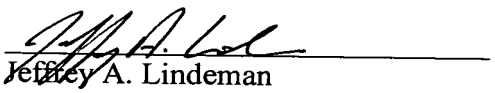
Second, while Larka discloses a method for detecting *H. pylori* using polyclonal antibodies, Larka unambiguously states that problems relating to cross-reactivity and strain variation with immunoassays for detection of H. pylori "rule out the use of monoclonal antibodies." (See Larka, Col. 1, lines 33-48). At the same time, Larka provides that while the invention is described with reference to the use of polyclonal antibodies, those skilled in the art will also recognize that two or more monoclonal antibodies could be used as an alternative to using polyclonal antibodies. Further, Larka defines the term "plurality of antibodies" to generically refer to a polyclonal antibody and a mixture of monoclonal antibodies. Larka, however, is totally silent about the use of antibodies having different specificity and about how to improve the sensitivity of the test. Accordingly, inasmuch as Larka fails to disclose the use antibodies for different antigens

and provides no enabling teaching how to use monoclonal antibodies, Larka fails to anticipate or render obvious the claimed invention. For these reasons, it is respectfully submitted that the rejection under 35 U.S.C. 102(b) should be reconsidered and withdrawn.

VI. Conclusion

Having responded to all rejections and objections set forth in the outstanding Office Action, it is submitted that new claims 54-91 are now in condition for allowance. An early and favorable Notice of Allowance is respectfully solicited. In the event that the Examiner is of the opinion that a brief telephone or personal interview will facilitate allowance of one or more of the above claims, the Examiner is courteously requested to contact Applicants' undersigned representative.

Respectfully submitted,



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